PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/001050	21.03.2005	21.10.2004

International Patent Classification (IPC) or both national classification and IPC
C07D243/24

Applicant
ARROW THERAPEUTICS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Goetz, G

Telephone No. +49 89 2399-8105

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/001050

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations

see separate sheet

D1: SHI Y-J ET AL: "Crystallization-induced asymmetric transformation: stereospecific syntehsis of L-768,673" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, no. 4, 22 January 1999 (1999-01-22), pages 909-918, XP004151316 ISSN: 0040-4020

D2: P. J. REIDER ET AL.: "Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of a Potent Peripheral CCK Antagonist" J ORG CHEM, vol. 52, 1987, pages 955-957, XP002330844

D3: WO 02/30912 A (MERCK SHARP & DOHME LIMITED; CHURCHER, IAN; NADIN, ALAN, JOHN; OWENS,) 18 April 2002 (2002-04-18)

D4: WO 95/14694 A (MERCK & CO., INC; BALDWIN, JOHN, J; CLAREMON, DAVID, A; ELLIOTT, JASON) 1 June 1995 (1995-06-01)

D5: BUTCHER J W ET AL: "Preparation of 3-Amino-1,4-Benzodiazepin-2-Ones Via Direct Azidation with Trisyl Azide" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 37, 9 September 1996 (1996-09-09), pages 6685-6688, XP004088066 ISSN: 0040-4039

D6: US-A-5 852 010 (GRAHAM ET AL) 22 December 1998 (1998-12-22)

D7: WO 93/17011 A (MERCK SHARP & DOHME LIMITED) 2 September 1993 (1993-09-02)

D8: WO 00/66106 A (THE REGENTS OF THE UNIVERSITY OF MICHIGAN; GLICK, GARY, D; OPIPARI, AN) 9 November 2000 (2000-11-09)

D9: WO 01/90084 A (MERCK SHARP & DOHME LIMITED; CASTRO PINEIRO, JOSE, LUIS; CHURCHER, IAN) 29 November 2001 (2001-11-29)

D10: WO 95/14471 A (MERCK & CO., INC; BALDWIN, JOHN, J; CLAREMON, DAVID, A; ELLIOTT, JASON) 1 June 1995 (1995-06-01)

D11: WO 2004/026843 A (ARROW THERAPEUTICS LIMITED; CARTER, MALCOLM; HENDERSON, ELISA; KELSEY,) 1 April 2004 (2004-04-01)

1. Novelty

1.1 The subject matter of present claim 1 is not novel having regard to the disclosure of D1 and D2 and D3:
Documents D1 and D2 disclose crystallization induced asymmetric transformation of

a compound according to formula (II) and/or (IIa) to a compound of formula (I). Reference is made to D1: scheme 2 (protecting group: CF3-CH2-) and to D2: scheme 2.
D11 discloses on pages 34 and 35 the procedure for crystallization induced asymmetric transformation whereby in the scheme on page 35 the process is exemplified for one particular compound.
The disclosure of D11 is thus novelty destroying for all claims 1 to 10 .
The subject matter of present claims 1 to 10 is thus not novel over the disclosure of D1, D2 and in particular D11 (PCT Article 33.2).

1.2 D3 to D10 disclose compounds falling within the scope of present formulae (II) and (IIa) of present claims 11 and 12 (reference is made to the passages cited in the search report).
The subject matter of present claims 11 and 12 is thus not novel over the disclosure of D3 to D10 (PCT Article 33.2).

2. Inventive step

2.1 In addition to the novelty objection raised against present claims 1 to 10 and objection of lack of inventive step is raised:
It is said on page 1 of the description that the process disclosed in D2 is "unsuccessfully applied to other benzodiazepine derivatives". It is thus evident for the skilled person that the claimed process will certainly depend on the specific structure of the benzodiazepine to be prepared and in particular on the educt of formula (II)/(IIa).
In the present case examples 1 to 9 demonstrate the claimed process. However, the structure of the educts and products of these examples is very restricted compared with the claimed scope: the protecting group R2 is in each case CH3-O-phenyl-CH2- and "--XR^4" represents either -NH_2 or the group as given in example 9.
Such a restricted formula cannot be regarded as being representative for all possible structures falling within the scope of the formulae (I), (II), and (IIa). It is evident for the skilled person that these examples only show a process where in particular R_2 represents a -CH2-phenyl-O-CH3-group. A generalization to other structures cannot be accepted in the absence of any further data.

The subject matter of present claims 1 to 10 and 11 to 12 insofar as novelty is given is thus not based on an inventive step (PCT Article 33.3).

3. The term "amino protecting group" has to be defined according to the definition given on page 6, lines 5 to 26(PCT Article 6).